(12) UK Patent Application (19) GB (11) 2 293 101 (13) A

(43) Date of A Publication 20.03.1996

(21) Application No 9518008.9

(22) Date of Filing 04.09.1995

(30) Priority Data
(31) 9418483 (32) 14.09.1994 (33) GB

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(51) INT CL[6]
A61K 31/557

(52) UK CL (Edition O)
A5B BKD B170 B180 B42Y B421 B422 B426 B48Y B482 B483 B59Y B595 B823 B826 B828 B835 B842
U1S S2414

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Br. J. Pharmacol. Vol. 107, (Proc. Suppl. Oct.) 1992, Abstract 90P Am. Rev. Respir. Dis., Vol. 141, No.4, Pt. 2, 1990, A735 Am. Rev. Respir. Dis., Vol. 141, No. 4, Pt. 2, 1990, A18

(58) Field of Search
UK CL (Edition N) A5B BKD
INT CL[6] A61K 31/557
ONLINE: MEDICINE, PHARM, WPI, JAPIO, CLAIMS

(54) Butaprost compositions for preventing pre-term labour

(57) Compositions designed to achieve constant butaprost concentrations of less than 1μM at the myometrium surface inhibit uterine contractions while avoiding undesired side-effects and are useful in preventing preterm labour. The compositions are in the form of infusions, pessaries, gels or tablets and may further include anti-microbials, e.g. metronidazole or cefuroxime and/or inhibitors of bacterial prostaglandins, e.g. nabumetone, flosulide and SC 58125.

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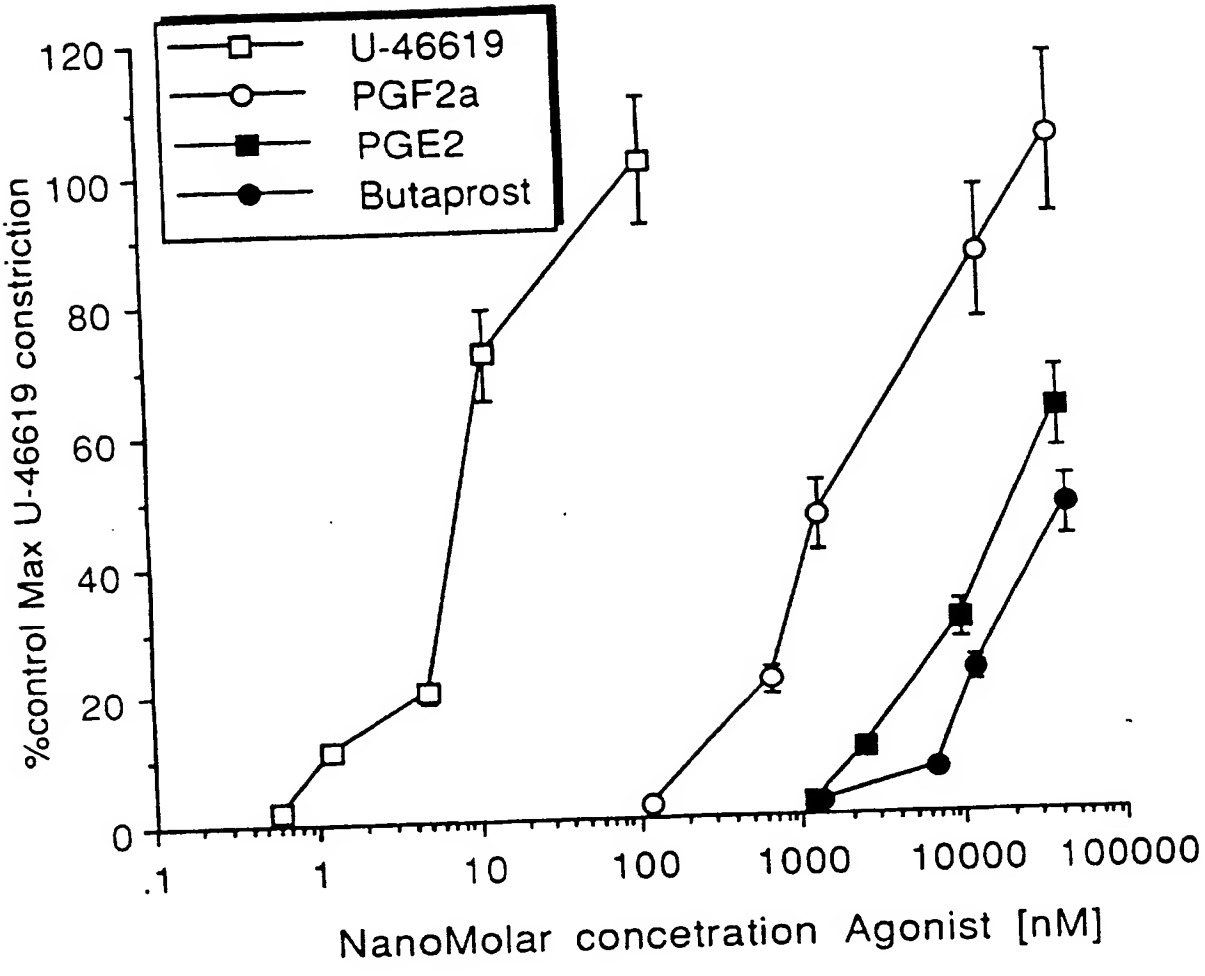
U-46619
PGF2a
PGE2
Butaprost
%control Max U-46619 constriction
120
100
80
60
40
20
0
.1
1
10
100
1000
10000
100000
NanoMolar concetration Agonist [nM]

COMPOUND FOR USE IN PRE-TERM LABOUR

Background to the invention

Field of the invention

This invention concerns the prevention of pre-term labour and in particular a compound for use in the management of pre-term labour.

Description of the Related Art

Pre-term delivery is a major cause of perinatal mortality and remains so, despite advances in obstetrics and neonatal care over the last decade. In any birth before 37 weeks of gestation, over 80% of neonatal deaths are due to early delivery rather than foetal abnormality. Aggressive treatment using existing tocolytic therapy may cause distress to the mother and foetus and many clinicians question the relevance of such therapy since there are few obvious benefits to the foetus and the possibility of risk to the patient is increased. The value of tocolytic therapy in pre-term labour thus remains doubtful since the incidence of pre-term delivery has not been reduced and prematurity is still the major contributing factor in neonatal mortality. The availability of modern technology allows the immature foetus to survive but the risk of permanent damage to the foetus and the cost of maintaining life are considerable. However, it is these advances in neonatal care, rather than improved tocolytic therapy, which have improved perinatal mortality rates in recent years.

Existing tocolytic therapies as reported in the literature include the use of β-adrenoceptor mimetics such as ritodrine, salbutamol and terbutaline, magnesium sulphate and calcium channel antagonists. Other treatments under investigation include the use of oxytocin antagonists and prostaglandin synthesis inhibitors. However, these existing treatments for pre-term labour lack efficacy and no novel treatments have emerged to alter the overall perinatal mortality and morbidity rate in the last decade. Clearly there is an urgent need to find a safe and effective way of halting pre-term labour and prolonging gestation.

Present prostanoid receptor classification states that each of the natural prostanoids has its own receptor termed the P receptor where that particular prostanoid is at least ten

times more potent than any of the other prostanoids. Thus the prostaglandin E_2 (PGE_2) sensitive receptor is termed the EP-receptor and likewise PGF_{2a} the FP-receptor; PGD_2 the DP-receptor; PGI_2, the IP-receptor and thromboxane A_2 (TXA_2), the TP receptor. The EP receptor, according to this classification based on selective agonists and antagonists in both functional and binding studies, has been subdivided into at least 4 major subtypes, the EP_1, EP_2 EP_3 and EP_4. Smooth muscle activation of the EP_1 and EP_3 receptors usually results in stimulation of activity, whereas activation of EP_2 receptors usually results in relaxation and EP_4 activation results in dilation of certain vascular preparations.

Functional studies on human myometrium show the presence of EP_1, EP_2 and EP_3 receptors on human myometrium. Selective prostaglandin agonists, antagonists and analogues as well as natural prostaglandins were used to characterise the receptors found on the human myometrium.

Senior et al. reports on the characterisation of receptors present on human myometrium in non-pregnant (Br J Pharmacol 1992 107, 215-221 and Br J Pharmacol 1991 102, 747-753) and term pregnant subjects (Br J Pharmacol 1993 108, 501-506). It was suggested that the potent inhibitory action of some synthetic prostaglandin analogues of these receptors could be useful in clinical hyperactivity states such as pre-term labour. Butaprost was mentioned as the most selective EP_2 receptor agonist used to date. Its use as a bronchodilator has been reported and it has been suggested for use in the treatment of bronchial asthma (Nials et al., Cardiovascular Drug Reviews 11 1993, 165-179). It has also been shown that butaprost is dilator on human uterine artery in the micromolar concentration range (2-6) but was at least 100-fold weaker than PGE_2 suggesting that EP_2 receptors are not involved in this response (Baxter et al., 1995, Br J Pharmacol., 116 1692-1696).

The present inventor has surprisingly discovered that contrary to these reports, butaprost is actually not a suitable compound for use in the management of pre-term labour as the literature articles would predict. Firstly, in vivo the half life of butaprost is very low and unpredictably, butaprost has a constrictor effect on the human umbilical artery. Surprisingly since butaprost has a weak dilator effect on the human uterine artery, this was not predictable. Thus this constrictor affect seems specific to the umbilical artery and is unusual which has the undesirable and dangerous side effect of causing foetal distress.

Summary of the invention

It has surprisingly been found that butaprost when locally applied in a consistent dosage can be useful in the management of pre-term labour without the associated dangerous or undesirable side effects outlined above. Accordingly, the current invention is based on the observation that for butaprost to be a useful tool in the management of pre-term labour it must be at a concentration of less than 1 micromolar at the myometrium and present at a consistent level over a long period of time.

Thus according to a first aspect of the invention there is provided a pharmaceutical composition comprising butaprost for the treatment of pre-term labour wherein the composition is adapted to ensure that the concentration of butaprost at the myometrium surface is substantially constant and at a concentration of less than 1micromolar.

Description of the Preferred Embodiments

In the research directed towards the study of receptors on the human myometrium, many EP agonists have been employed but few show absolute selectivity for the individual EP_1, EP_2 and EP_3 receptor types. Senior et al. (Br J Pharmacol 1993, 108, 501-506) reports that butaprost is the most selective EP_2 agonist used to date but, although inhibiting myometrial activity it was reported by Lawrence & Jones (Br J Pharmacol 1992, 105, 817-824) to have a constrictor effect on chick ileum and thus would not be indicative of any clinically useful role in pre-term labour management. This, coupled with the recent observations about a contractile effect on the umbilical artery effectively rule out butaprost as a serious approach to the management of pre-term labour. The full range of prostanoid receptors implicated in this response are not known but it is thought that thromboxane receptors account for at least 50%.

The observations that the concentrations of butaprost actually required for myometrial inhibition is less than the concentrations for toxicity and constrictor activity to become apparent lie at the heart of the invention. The problem is one of ensuring that the concentration of butaprost at the myometrium is correct to have advantageous and not disadvantageous effects.

The pharmaceutical composition of the present invention is adapted to achieve this aim. Thus, the concentration of butaprost at the myometrial surface is achieved over long periods of time by various methods. For example, a patient could be given a continuous infusion of butaprost. More preferable are controlled release formulation such as pessaries, gels and tablets. These have an added advantage of being locally (intravaginally) applied.

Most preferred are controlled release compositions comprising butaprost and a polymeric composition according to GB 2047094B, the contents of which are incorporated herein by reference.

Suitable dosages will depend on individual cases but generally will be in the range 10nM min^{-1}. This dosage will maintain the necessary concentration of butaprost at the myometrial surface and can be maintained as long as necessary from hours to weeks depending upon the needs of the patient.. Preferably, retrieval devices are included if the composition takes the form of a pessary.

It has often been difficult to diagnose and manage pre-term labour which has led to inappropriate use of drugs. In some cases pre-term delivery is induced by pathogens present in the maternal reproductive tract. In such cases, appropriate antimicrobial therapy is provided. This is an area where treatment is promising in the management of pre-term labour. Conveniently then, the pharmaceutical composition of the present invention also includes an antimicrobial for the management of this infection. Currently used antimicrobials which may be applied topically for this condition and are thus suitable for inclusion in a controlled release locally applied formulation such as a pessary, include metronidazole and concentrations in the range of 1mg Kg^{-1} bodyweight $hour^{-1}$ are desirable. It would also be useful to administer butaprost intravaginally as described hereinabove together with systemically administered antimicrobials e.g. cefuroxime either by infusion or orally.

Additionally, pre-term labour is often induced by bacterially induced prostaglandins. The enzyme prostaglandin G/H synthase-2 (PG HS-2) also named cyclo-oxygenase 2 is responsible for this synthesis and hence, the pharmaceutical composition of the invention together with or instead of the antibiotic also includes an inhibitor of this enzyme. Inhibitors include nabumetone, flosulide and SC 58125 and a concentration range of 0.01-0.1mM is preferable.

It will be appreciated by a person skilled in the art that a person in pre-term labour can be supplied with any combination of the above described pharmaceutical compositions depending upon whether or not there is an infection of the maternal reproductive tract when the patient presents herself.

The invention will now be illustrated by way of Example with reference to Figure 1 which shows the effect of various prostanoids on the human umbilical artery in vitro.

Example 1

Inhibitory activity of butaprost on human myometrium

Method

Samples of gestational human myometrium (term pregnancy) from the lower segment were removed at elective Caesarean section (non-labouring) and set up in a superfusion apparatus (n = 8). Tissues were tested for sensitivity by administering PGE_2 (5nM) as a bolus dose and only those strips which responded with a biphasic or inhibitory response were used. The concentration of butaprost was administered in the superfusate over a 15 min period and the number of tissues responding with complete inhibition of myogenic activity was recorded.

Results

Butaprost at a concentration of 0.1 micromolar administered over a 15 min period caused complete inhibition of myogenic activity. The mean recovery time for the myogenic activity after cessation of superfusion of butaprost (0.1micromolar) was 22 % 5 mins. No stimulation of uterine activity was noted at any dose of butaprost investigated.

The EP_2 agonist, butaprost, is a potent inhibitor of human myometrial activity and is devoid of stimulant action.

The results are shown in Table 1 below.

TABLE 1

The % of samples of human myometrium from pregnant donors responding to the EP_2 agonist, butaprost, at various concentrations.

Concentration of butaprost	No response	Complete inhibition
1nM	100	0
10nM	75	25
0.1μM	0	100
1μM	0	100
10μM	0	100

Example 2

Umbilical Artery - effect of butaprost and other prostanoids

Method

The specimens of umbilical cord were set up in the laboratory within 120 mins of delivery of the foetus. The artery from the central section of the cord was dissected free of connective tissue and immersed in Krebs solution containing indomethacin 2.79 micromolar gassed with 2.5% O_2 8% CO_2 89.5% N_2 at 37°C. Cumulative dose-response curves were obtained from agonists.

Results and Conclusions

Preliminary results using various prostanoid agonists are shown in Figure 1 (n = 4).

The EC_{50} values for other agonists used are shown in Table 2. The thromboxane mimetic, U46619, is a potent constrictor of human umbilical artery in vitro, suggesting the presence of TP receptors on this tissue. The constrictor effects of PGF_{2a} and PGE_2 occur at much higher concentrations, suggesting that these compounds may be acting through the TP receptors rather than FP and EP receptors on this tissue. The constrictor effect of butaprost is surprising, since it is known to act selectively through EP_2 receptors which normally show relaxant effects. As can clearly be seen this constrictor effect of butaprost is only apparent at concentrations greater than 1μM.

TABLE 2

The EC_{50} values for prostanoid agonists on human umbilical artery in vitro.

Prostanoid	EC_{50} (μM)
U46619	0.007
PGF_{2a}	5
PGE_2	20
Butaprost	60

CLAIMS

1. A pharmaceutical composition for the treatment of pre-term labour comprising butaprost wherein the composition is adapted to ensure that the concentration of butaprost at the myometrium surface is substantially constant and at a concentration of less than 1 micromolar.

2. A pharmaceutical composition according to claim 1 which is an infusion.

3. A pharmaceutical composition according to claim 1 adapted for controlled release.

4. A pharmaceutical composition according to claim 3 which is a pessary.

5. A pharmaceutical composition according to claim 4 wherein the pessary includes a retrieval device.

6. A pharmaceutical composition according to any preceding claim which further includes an antimicrobial.

7. A pharmaceutical composition according to claim 6 wherein the antimicrobial is metronidazole.

Patents Act 1977 — Examiner's report to the Comptroller under Section 17 (The Search report)	Application number GB 9518008.9
Relevant Technical Fields (i) UK Cl (Ed.N) A5B BKD (ii) Int Cl (Ed.6) A61K 31/557	Search Examiner MR S J PILLING Date of completion of Search 27 NOVEMBER 1995
Databases (see below) (i) UK Patent Office collections of GB, EP, WO and US patent specifications. (ii) ONLINE: MEDICINE, PHARM, WPI, JAPIO, CLAIMS	Documents considered relevant following a search in respect of Claims :- 1 TO 7

Categories of documents

X: Document indicating lack of novelty or of inventive step.

Y: Document indicating lack of inventive step if combined with one or more other documents of the same category.

A: Document indicating technological background and/or state of the art

P: Document published on or after the declared priority date but before the filing date of the present application.

E: Patent document published on or after, but with priority date earlier than, the filing date of the present application.

&: Member of the same patent family, corresponding document.

Category	Identity of document and relevant passages	Relevant to claim(s)
X	DE 3810081 A (BAYER AG) (05.10.89) see WPI Abstract Accession No 89-293672/41	1
X	Br. J. Pharmacol. Vol 107, (Proc. Suppl. Oct) 1992, Yeardley H L et al, "A comparison of the inhibitory effects of prostanoid EP_2 receptor agonists and $ß_2$ - adrenoreceptor agonists.." Abstract 90P	1
X	Am. Rev. Respir. Dis., Vol 141, No 4, Pt 2 1990, Peck M J et al, "Effects of butaprost and prostaglandin E1 against E. Coli Endotoxin-induced lung injury in anaesthetized sheep" A735	1, 2
X	Am. Rev. Respir. Dis., Vol 141, No 4, Pt 2, 1990, Francis D L et al, "Effect of butaprose and isoprenaline during periods of acute alveolar hypoxia in anaesthetized sheep.", A18	1, 2

Databases: The UK Patent Office database comprises classified collections of GB, EP, WO and US patent specifications as outlined periodically in the Official Journal (Patents). The on-line databases considered for search are also listed periodically in the Official Journal (Patents).